

AMENDMENTS TO CLAIMS

CLAIMS 1, and 2 (CANCELED)

CLAIM 3 A process for treating reversible blood vessel occlusions in a human being who has suffered an ischemic cerebrovascular accident (stroke) with compromised blood flow and subsequent leakage of nitrogen into the intramitochondrial space of affected tissues causing an impairment in oxidative metabolism in said mitochondria, which comprises administering through a face mask the inhalation of a nitrogen free gas mixture of oxygen and helium, each at 20-80% complimentary concentrations with exhalations being shunted through a one-way flutter valve into the ambient atmosphere to effect a 50-90% or more washout of nitrogen from the body and body water until blood flow is restored to the compromised area and a subsequent washout of nitrogen from the affected tissues and mitochondria permits the return of said ischemic tissues to a state of oxidative metabolism. (NEW)

Claim 4, The process of claim 3 where said treatment is implemented as soon as possible following admission to the hospital and continued for 30 minutes up to 72 hours to assure optimum therapy and minimize cell death. (NEW)

CLAIM 5. The process of claim 4 wherein the gas mixture is 30% oxygen and 70% helium. (NEW)

CLAIM 6. The process of claim 3, wherein the gas mixture is 30% oxygen and 70% helium. (NEW).

REBUTAL TO REJECTION NOTICE:

Applicant respectfully traverses the rejection as applied to the newly added claims as being obvious under US patent 6001332 to Garrett in view of the Textbook of Physiology (Guyton) and in further view of US patent 6899103 to Hood. Reconsideration is respectfully requested.

Garrett discloses various helium-oxygen mixtures for treating asthma, obstructive airway disease, and MRI imaging, presented with extensive detail. He indicates that there are difficulties with these mixtures which he proposes to remedy with the addition of carbon dioxide (all 12 claims). At column 2 lines 3-7, he states an additional benefit of a helium-oxygen mixture is that when administered to patients with an acute myocardial infarction the myocardium appears to be stabilized reducing the risk of ventricular arrhythmias. This is the only reference to myocardial infarction in Garrett. You can not tell the make-up of the helium-oxygen mixture to which Garrett refers or how the patient was treated. Presumably Garrett would feel that the addition of carbon dioxide would be of benefit to this therapy, but no discussion was forthcoming. Applicant conducted a literature search [Library of Medicine—Pubmed] and found no publications for the author Michael E. Garrett, and the citations which included helium-oxygen and heart included only three references by Pifarre et al. They studied ventricular arrhythmias

in dogs, not humans. Their surgical procedure involved ligation and severing of the left circumflex coronary artery, a permanent occlusion unlike the reversible vascular occlusions of the instant invention. The most effective formulation which they tested was 30% oxygen, 20% helium and 50% air, the latter would make the inhaled mixture enriched by 39.5% nitrogen and this would totally preclude the nitrogen washout process of the instant invention. See page 5, lines 3 and four "Any gas mixture which has as its main purpose the washout of nitrogen from the body would surely be devoid of nitrogen per se". Pifarre concludes that the oxygen-helium mixtures in dogs with acute coronary occlusions act to (1) increase the coronary collateral circulation; (2) increase the coronary sinus blood flow; (3) reduction in the incidence of ventricular fibrillation; and (4) reduction in the size of the infarcted area. Clearly, none of these mechanisms fits in any way with the nitrogen washout process of the instant invention, but number (3) above, reduction in the incidence of ventricular fibrillation does fit with Garrett Col 2 lines 6 and 7 "the myocardium appears to be stabilized reducing the risk of ventricular arrhythmias." Therefore, applicant submits that Garrett, by way of Pifarre teaches away from the instant invention in its broad sense and specifically the claim embodiments which are directed to nitrogen washout from oxygen -helium gas mixtures in reversible vascular occlusion in stroke or heart attack with compromised or occluded blood flow and impairment of oxidative metabolism.

Examiner allows that what is NOT disclosed by Garrett is delivering the helium-oxygen

gas mixture to effect a 50-90% or more washout of nitrogen gas from the body, body water, ischemic tissues, and mitochondria in order to allow the reuptake of oxygen into hypoxic mitochondria and restore oxidative metabolism to affected tissues following a reversible vascular occlusion in a cerebrovascular accident, the administration of said gas being from a suitable supply source and being implemented during patient transport or upon admission to the hospital as quickly as possible following the event and continued for a minimum of 30 minutes up to 72 hours to assure optimum therapy and minimize cell death. What is taught by Guyton is the use of a decompression chamber, or hyperbaric chamber, to treat a diver who has been beneath the sea long enough so that large amounts of nitrogen have dissolved in his body. Guyton teaches that if a diver is brought to the surface slowly, or placed in a decompression chamber, or hyperbaric chamber where it is known to deliver oxygen helium gas mixtures so the dissolved nitrogen is eliminated through his lungs rapidly enough to prevent decompression sickness. Approximately two-thirds of the total nitrogen is liberated in one hour and about 90% in six hours (which teaches that method is carried out to effect a 50-90% or more washout of nitrogen from the body and carry out the method for a minimum of 30 minutes up to 72 hours).

Although applicant's specification does cover long periods of therapy, it is clear that applicant indicated on page six lines 10-12 "improved clinical benefits might be expected from nitrogen washouts of 75-90% or more and this could require 60 -90 minutes or longer" That certainly does not fit with the 6 hours plus for

90% nitrogen washout in the Guyton chamber. Moreover, on page 7 lines 4-8 applicant states. "The extended time frame beyond 1-2 hours for inhaling the gas mixture and continuing nitrogen washout may be a clinical decision to ensure that mitochondrial metabolism and mitochondrial membrane repair, function and stability have been fully restored to levels wherein the re-introduction of high concentrations of inhaled nitrogen would not re-aggravate the injury." Clearly, applicant indicates that the nitrogen washout process involves a rapid 60-90 minutes acute (90%+) washout phase and a continuing time frame washout phase to allow for optimum tissue recovery.

Guyton's subjects are not ill and the bends is a condition which does not include the strokes or heart attacks of the instant invention. The proposal for using hyperbaric chambers early in the treatment of acute strokes or heart attacks suffers from the fact that such patients are very unstable and physicians need to have immediate access to said patients in order to treat emergencies which might, and do develop. Patients sequestered in hyperbaric chambers are trapped therein until a safe release and lowering of the intrachamber pressure can be achieved and this could require 5-15 minutes or longer during which time the patient would be denied proper medical attention and could therefore die. This alone, could lead to a medical malpractice nightmare which would render these chambers unsatisfactory. These bulky and expensive chambers are relatively unavailable and would also be impractical in

that they would be limited to one patient at a time. Therefore, hospitals would have perhaps five or more available to cover multiple patient arrivals on the same day and/or to keep patients in them for extended periods of time. Finally, two recent review articles are germane to this discussion. Oppel et al conducted a review of the scientific evidence on the value of hyperbaric oxygen treatments in traumatic brain injury and strokes. His conclusions were “The scientific literature up to August 2001 does not support the use of hyperbaric oxygen for traumatic brain injuries and strokes. Also concluded, “In balance, the strongest papers indicated either no effect or harm from hyperbaric oxygen when used to treat TBI or stroke.” Rusyniak et al concluded, “Although our HBO (hyperbaric oxygen) protocol appears feasible and safe, it does not appear to be beneficial and may be harmful in patients with acute ischemic stroke.”

Further on hyperbaric chambers and Hood. Applicant has no argument concerning examiners reference to the “golden hour” which is emphasized by Hood, but then that is and has been the purpose of ambulances and EMS vehicles for decades. Applicant indicates only that the nitrogen washout process “could” be started during patient transport, but doesn’t require or claim it. Moreover, if the decision is made at some future date to implement nitrogen washout during patient transport, it would be utilizing the inexpensive technology of the instant invention not using cumbersome hyperbaric chambers. A minor point perhaps but Hood’s reference to strokes makes no

differentiation as to type of stroke and therefore automatically includes all strokes; Applicant specifically limits his claims to reversible vascular occlusions. Reversible vascular occlusions are ischemic strokes and represent 80% of the total; the other 20% are hemorrhagic strokes and are untreatable and unclaimed by the instant invention. Hood's treatments are merely designed to aid survival of the patient until he reaches the hospital. Only then can specific therapies be instituted.

Relative to all three references of the examiner is his statement that it is inherent that exhaled gases from a patient are shunted into ambient atmosphere. Applicant stresses in the specification and in claim 3 that the inhaled gas mixture is nitrogen free or devoid of nitrogen. Therefore if you inhale any nitrogen you are not practicing the invention. When you normally exhale in a room, you subsequently re-breathe nitrogen into your lungs and respiratory tract and as well inhale additional nitrogen from the room atmosphere. In Guyton's hyperbaric chamber, nitrogen re-breathing is required as the nitrogen from the body equilibrates with the hyperbaric oxygen in the chamber. Therefore, Guyton does not follow the dictates of the instant invention specification or claims. With Hood the case is even worse. Clearly the dimensions of Hood's hyperbaric transport chamber are very much smaller still than a standard hyperbaric chamber. Indeed, Hood Col 15, lines 1-3 speaks of the need to sense carbon dioxide (CO₂) levels and open an exhaust valve to dump stale air. This indicates a very high level of re-breathing into a very small ambient atmosphere thereby precluding Hood's

system form achieving significant nitrogen washout. Indeed, in surgical suites it is common for the ambient atmosphere to be a closed system wherein anesthetic gases are re-breathed to keep operating room personnel insulated from dangerous gases, and in this case carbon dioxide build-up in the system is precluded by the use of absorbent granules. Thus, depending on the volume of the ambient atmosphere and its composition it is possible to re-breathe nitrogen in many situations including the hyperbaric chambers of Guyton and Hood. Contrast these limitations to the comprehensive level of no nitrogen in the inhaled gas mixture coupled with nitrogen washout with each breath and lack of re-breathing of nitrogen by use of face masks with one-way flutter valve exhalation ports as claimed for the instant invention.

For general information: The instant invention fits nicely with the current practice of medicine in treating strokes. After initial symptoms, patients with significant symptoms are rushed to the hospital, with an arrival time of about 45 -60 minutes. Appreciating the need for speedy therapy, the patient is quickly stabilized and evaluated for various neurological and coma scores. Then, with dispatch the patient is taken to imaging to make an assessment as to whether the stroke is ischemic (reversible) or hemorrhagic non-reversible). [note: hospitals are beginning to establish a radiological computerized tomography suite adjacent to the ER room to speed-up the imaging times]. This distinction is crucial to patient treatment since hemorrhagic stroke patients cannot be administered clot-buster pharmaceuticals. On the other hand, many of the

ischemic stroke patients are candidates and they need to have these drugs on board rapidly after CT scanning , i.e.within 180 minutes of first symptoms and optimum therapy would have the CT data available by 90 minutes from first symptoms.

Marler, in a combined study publication on thrombolytics stressed “time is brain”. The point of this is that after administration, thrombolytics can often provide effective re-flow within two hours, and instituting the instant invention simultaneously with the administration of the thrombolytics will provide 90% or more washout of nitrogen from the body by two hours. Hence, the blood levels of nitrogen are minimized to an extent such that blood delivered to the re-flowed ischemic region can immediately begin to flush out that nitrogen entrapped in the stroke affected tissues and mitochondria.

In conclusion:

- 1) Garrett does not provide any mechanism to wash nitrogen out of the ischemic tissues and mitochondria and the sole literature in the field (Pifarre) teaches away from the nitrogen washout of the instant specification and claim 3 .
- 2) Guyton’s 6 hour requirement for 90% washout of nitrogen is inoperable with current stroke therapy practice. Hyperbaric oxygen in the initial hours following a stroke requires separation of the patient from the attending physician and portends a likely malpractice nightmare. Finally, two recent review articles do not recommend hyperbaric oxygen in the treatment of stroke

3) Hood describes a system which only purports to improve survival of patients (mainly battlefield casualties) during transport and says nothing as to how they are treated thereafter. The instant invention claims only treatments which are initiated after admission to the hospital.

Finally there have been some important wording changes on the claims. Support for these changes is present in applicant's specification and is itemized below.

a. CLAIM 3, the addition of the use of a face mask to administer the helium-oxygen mixture. See page 7 , lines 17-19 "Multiple systems could prove useful at various stages of the nitrogen washout process. The most effective would employ a face mask inhalation device with a one-way flutter valve to shunt exhaled gases into the ambient atmosphere."

b. CLAIM 3 also adds with exhalations being shunted through a one-way flutter valve into the ambient atmosphere. See page 7, lines 17-19 above.

c. deletion of 100% oxygen and using formulations each at 20-80% complimentary concentrations of oxygen and helium. See Page 5, lines 4-6: "Oxygen would be a requisite gas, and could be used at 100%, but that might not foster the fastest washout of nitrogen from the body or mitochondria".

Page 6 (on the need for some helium) lines 18-21. " This reverse gradient would also extend to that nitrogen trapped in the mitochondria, and it would be expected that the

small molecule of helium would easily gain access to the interior of the affected mitochondria to further hasten the nitrogen washout”.

These two specification statement speak to the need and benefit for helium in the gas mixture. Therefore, in keeping with the goal of claiming only the best embodiments of one's invention, applicant has elected to remove 100% oxygen as part of the claimed material.

For general support of lines 1-4 and 8-11 of claim 3, see page 6, lines 12 -22 and page 7 line 1 “ If, at these or some delayed time frames, blood flow is re-established to the ischemic tissues, there would exist a higher concentration of nitrogen in the water and mitochondria of the ischemic region than in the surrounding tissues which had been undergoing nitrogen washout. As a result, a reverse partial pressure gradient for nitrogen would exist which would promote the removal of nitrogen from the ischemic region back into the circulating blood and to the lungs for exhalation. This reverse gradient would also extend to that nitrogen trapped in the mitochondria, and it would be expected that the small molecule of helium would easily gain access to the interior of the affected mitochondria to further hasten the nitrogen washout. Along with helium, oxygen would then regain access into mitochondria returning said mitochondria to a state of oxidative metabolism with a concurrent return of mitochondrial membrane integrity and selectivity.”

Respectfully there is nothing in the prior art references which address the instant invention either in general or especially in detail. Generally all three teach away from the invention as it is presented and its likely method of use in clinical medicine. The Pifarre articles teach away from the statement on heart attacks by Garrett, especially since the most effective formulation contain nitrogen, and the mechanism of beneficial effect espoused by Pifarre was an increase in collateral circulation. In addition to several glaring inadequacies and problems with the Guyton and Hood hyperbaric chambers, two reviews in the literature indicate that hyperbaric oxygen does not work in the treatment of stroke and indeed, may be harmful. Hence, these prior art references have no pragmatic utility and, in fact are inoperative in the treatment of ischemic stroke as detailed in applicant's claims 3,4,5 and 6. Therefore applicant respectfully requests reexamination and reconsideration based on this new submission and new claim presentation and pleads for the allowance of claims 3,4,5 and 6 as presented.